Patisiran: Technetium Uptake by Scintigraphy

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SUMMARY

- As part of the APOLLO-B study protocol, technetium scintigraphy was collected in a subset of patients, as an optional exploratory imaging assessment, to assess cardiac amyloid involvement. All 37 patients in the patisiran arm with evaluable scintigraphy data (100%) had either no change from baseline or a reduced Perugini grade at Month 12.[1,2]
- In the APOLLO-B study, both the patisiran and placebo arms had similar frequencies of AEs (91% and 94%) and SAEs (34% and 35%) at Month 12. In the safety analysis, there were 5 deaths (3%) in the patisiran arm and 8 deaths (4%) in the placebo arm.[3]

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CLINICAL DATA

APOLLO-B Study

APOLLO-B was a multicenter, randomized (1:1), double-blind, placebo-controlled, phase 3 study designed to evaluate the efficacy and safety of IV patisiran 0.3 mg/kg every 3 weeks (n=181) versus placebo (n=179) in patients with ATTR with cardiomyopathy, including both hATTR and wtATTR. The primary endpoint was the change from baseline in the 6-MWT at 12 months. After the 12-month double-blind treatment period, all patients received patisiran in an open-label extension period.[3]

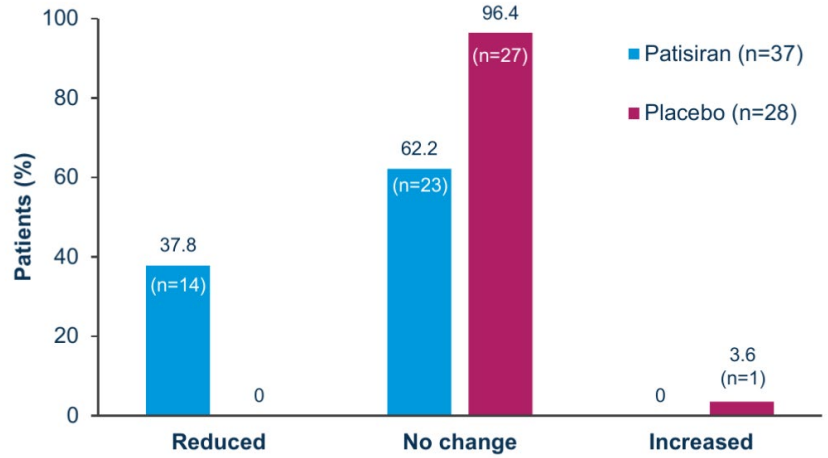
As part of the APOLLO-B study protocol, technetium scintigraphy was collected in a subset of patients, as an optional exploratory imaging assessment, to assess cardiac amyloid involvement. Based on local practice standards, either ^{99m}Tc-DPD, ^{99m}Tc-PYP, or ^{99m}Tc-HMDP could be used as the tracer.[1]

Planned Technetium Scintigraphy Cohort

At Month 12, there were 37 patients in the patisiran arm and 28 patients in the placebo arm that had evaluable technetium scintigraphy data. **Figure 1** shows the change from baseline in Perugini grade at Month 12 in all evaluable patients. In the patisiran arm, there were 14 (37.8%) patients that experienced a reduction from baseline of ≥1 Perugini grade, which included 3 (8.1%) patients that experienced a reduction by ≥2 Perugini grades at Month 12. The remaining 23 (62.2%) patients experienced no change from baseline in Perugini grade at Month 12.[2]

Among 28 evaluable patients in the placebo arm, no patients had a Perugini grade that was reduced from baseline at Month 12.[2]

Figure 1. Change from Baseline in Perugini Grade at Month 12 in All Evaluable Patients.[2,a]



[a]Analysis includes patients in the patisiran (n=37) and placebo (n=28) arms from the full analysis set with evaluable data at baseline and Month 12. 40 patients in the patisiran group and 37 patients in the placebo group were evaluated at baseline. 37 patients in the patisiran group and 28 patients in the placebo group were evaluated at Month 12.
From Kale et al.[2]

Safety Results

AEs reported in APOLLO-B at the end of the 12-month treatment period are summarized in **Table 1**. The majority of AEs were mild or moderate in severity. AEs that were reported in ≥5% of patients in the patisiran arm and seen ≥3% more frequently with patisiran than with placebo were IRRs (12% vs. 9%), arthralgia (8% vs. 4%), and muscle spasm (7% vs 2%).[3]

Table 1. Summary of Adverse Events in APOLLO-B at 12 Months.[3]

Event, n (%)	Patisiran (N=181)	Placebo (N=178)
Any AE	165 (91)	168 (94)
Any serious AE	61 (34)	63 (35)
Any severe AE	47 (26)	52 (29)
Any AE leading to treatment discontinuation	5 (3)	5 (3)
Deaths (safety analysis)[a]	5 (3)	8 (4)

Abbreviations: AE = adverse event; HF = heart failure.
[a]Deaths in the patisiran arm included sudden cardiac death (1 patient) and death from HF, pancreatitis, Covid-19, and undetermined cause (1 patient each). Deaths in the placebo arm included death from HF (3 patients), undetermined cause (2 patients), and cholangitis, infection, and pancreatic cancer (1 patient each).

PUBLISHED LITERATURE

The following information provides an overview of published medical literature evaluating the effect of patisiran as assessed by technetium scintigraphy. It is not intended to be an all-inclusive list or summary of relevant publications, abstracts, and manuscripts.

Rettl R, et al. Reduction in ^{99m}Tc-DPD myocardial uptake with therapy of ATTR cardiomyopathy. *Amyloid*. 2024;31(1):42-51. doi:10.1080/13506129.2023.2247136[4,5]

- A study was conducted as part of a prospective heart failure registry at the Medical University of Vienna, Austria to assess the effect of RNAi therapy (patisiran or inotersen) on myocardial amyloid load in patients with hATTR with cardiomyopathy diagnosed between February 2019 and January 2021. Patients underwent ^{99m}Tc-DPD scintigraphy and quantitative SPECT/CT imaging before and after 12 months of treatment with RNAi therapy.

- Among 9 patients treated with RNAi therapy, 5 patients received patisiran. At baseline, the mean (SD) age of the patients treated with patisiran was 65.6 (6.2) years, and 3 patients were NYHA class ≥ III. All 5 patients were classified as Perugini grade 3.
- During follow-up assessments, 4 patients were classified as Perugini grade 3 and 1 patient was classified as Perugini grade 2 among those treated with patisiran.

Tingen HSA, et al. Cardiac [^{99m}Tc]Tc-hydroxydiphosphonate uptake on bone scintigraphy in patients with hereditary transthyretin amyloidosis: an early follow-up marker? *Eur J Nucl Med Mol Imaging*. 2024;51(3):681-690. doi:10.1007/s00259-023-06459-y[6]

- A retrospective cohort study was conducted to evaluate the utility of ^{99m}Tc-HDP bone scintigraphy in assessing the treatment efficacy of patisiran and TTR stabilizers in patients with hATTR with cardiomyopathy. Study participants included patients treated with patisiran at the National Amyloidosis Centre of Expertise of the University Medical Centre Groningen in the Netherlands with a baseline bone scintigraphy and at least one follow-up bone scintigraphy.
- The study analyzed two groups: one group treated with patisiran (with or without additional TTR stabilizer) and one group treated with a TTR stabilizer only. The patisiran group included 20 patients who received patisiran 0.3 mg/kg by IV infusion every 3 weeks for at least 11 months. Eight patients (40%) received additional treatment with tafamidis (20 mg daily for 7 patients, 80 mg daily for 1 patient), and 3 patients received additional treatment with diflunisal (250 mg twice daily).
- At baseline, 2 (10%) patients were Perugini grade 1, 7 (35%) patients were Perugini grade 2, and 11 (55%) patients were Perugini grade 3. The median follow-up duration was 29 (15 to 34) months. At follow-up, 3 patients demonstrated a decrease in Perugini score of 1 point, and 2 patients demonstrated a decrease of 2 points.

Fontana M, et al. Reduction in CMR derived extracellular volume with patisiran indicates cardiac amyloid regression. *JACC Cardiovasc Imaging*. 2021;14(1):189-199. doi:10.1016/j.jcmg.2020.07.043[7]

- A study was conducted to determine the effect of patisiran on the cardiac amyloid load as measured by cardiac magnetic resonance and extracellular volume mapping in cases of transthyretin cardiomyopathy. All patients with hATTR that were enrolled in a United Kingdom patisiran early access program between July 2017 and November 2018 were invited to participate in a prospective clinical follow-up program. The program included functional assessments, comprehensive investigations, routine biochemistry, and cardiac assessments including ^{99m}Tc-DPD scintigraphy at the start of therapy and on an annual basis thereafter.
- All patients received patisiran 0.3 mg/kg by IV infusion every 3 weeks. Analyses were conducted in 16 patients with cardiomyopathy, of which 12 received concomitant diflunisal 250 mg twice daily throughout the study.
- After 12 months of treatment, there was a reduction in cardiac uptake of ^{99m}Tc-DPD scintigraphy of 19.6% (IQR: 9.8% to 27.1%) in treated patients. Fifteen of the 16 patients treated had a reduction in cardiac uptake of ^{99m}Tc-DPD, and in 1 patient the cardiac uptake was unchanged. The reduction in cardiac uptake was usually accompanied by a reduction in soft tissue and muscle uptake and an increase in bone signal.
- Overall, patisiran was well tolerated. No patient discontinued treatment during the period of assessment. Mild IRRs occurred in 4 patients and were self-limiting in each case. There were 8 SAEs during the period of assessment, none of which were deemed related to treatment.

Groothof D, et al. Regression of bone-tracer uptake in cardiac transthyretin amyloidosis. *Mayo Clin Proc*. 2020;95(2):417-418. doi:10.1016/j.mayocp.2019.10.036[8]

- A case report detailed the use of ^{99m}Tc-HMDP bone scintigraphy to evaluate treatment efficacy in a 68-year-old white male diagnosed with hATTR, caused by the V50M variant, in September 2009. At the time, echocardiography did not suggest cardiac involvement, and TTR-stabilizing treatment was started.
- In November 2012, bone scintigraphy showed moderate myocardial tracer uptake (grade 1), indicating some cardiac involvement despite no substantial echocardiographic changes compared with the scan taken in 2009.
- In December 2014, echocardiography revealed thickening and sparkling of the interventricular septum (13 mm) and left-ventricular posterior wall (13 mm), diastolic dysfunction, and cardiac bone-tracer uptake had also increased (grade 2), confirming progression of cardiac involvement.
- A bone scintigraphy conducted in December 2015 showed marked cardiac radiotracer uptake (grade 2). At that time, the patient enrolled in a study of inotersen in hATTR, during which TTR-stabilizing treatment was discontinued and the patient received placebo. In March 2017, the patient continued in the open-label extension study and received inotersen. In December 2017, TTR-stabilizing treatment was resumed.
- In April 2018, inotersen was discontinued, and treatment with patisiran was started upon the patient's request. After 14 months of inotersen and 7 months of patisiran, cardiac bone-tracer uptake had completely disappeared (grade 0). The patient's overall status had improved.

ABBREVIATIONS

6-MWT = 6-minute walk test; ^{99m}Tc-DPD = ^{99m}technetium-3,3-diphosphono-1,2-propanodicarboxylic acid; ^{99m}Tc-HDP = ^{99m}technetium-hydroxydiphosphonate; ^{99m}Tc-HMDP = ^{99m}technetium-hydroxymethylene diphosphonate; ^{99m}Tc-PYP = ^{99m}technetium-pyrophosphate; AE = adverse event; ATTR = transthyretin amyloidosis; hATTR = hereditary transthyretin amyloidosis; HF = heart failure; IQR = interquartile range; IRR = infusion-related reaction; IV = intravenous; NYHA = New York Heart Association; RNAi = ribonucleic acid interference; SAE = serious adverse event; SD = standard deviation; SPECT/CT = single photo emission computed tomography/computed tomography; TTR = transthyretin; wtATTR = wild-type transthyretin amyloidosis.

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REFERENCES

1. Protocol for: Maurer MS, Kale P, Fontana M, et al. Patisiran treatment in patients with transthyretin cardiac amyloidosis. *N Engl J Med*. 2023;389(17):1553-1565. doi:10.1056/NEJMoa2300757
2. Kale P, Maurer MS, Fontana M, et al. Exploratory Analyses from APOLLO-B, a Phase 3 Study of Patisiran in Patients with ATTR Amyloidosis with Cardiomyopathy. Presented at: Heart Failure Society of America (HFSA) Annual Scientific Meeting. September 30–October 3, 2022. Washington, DC, USA.
3. Maurer MS, Kale P, Fontana M, et al. Patisiran treatment in patients with transthyretin cardiac amyloidosis. *N Engl J Med*. 2023;389(17):1553-1565. doi:10.1056/NEJMoa2300757
4. Rettl R, Calabretta R, Duca F, et al. Reduction in 99mTc-DPD myocardial uptake with therapy of ATTR cardiomyopathy. *Amyloid*. 2024;31(1):42-51. doi:10.1080/13506129.2023.2247136
5. Supplement to: Rettl R, Calabretta R, Duca F, et al. Reduction in 99mTc-DPD myocardial uptake with therapy of ATTR cardiomyopathy. *Amyloid*. 2024;31(1):42-51. doi:10.1080/13506129.2023.2247136
6. Tingen HSA, Tubben A, Bijzet J, et al. Cardiac [99mTc]Tc-hydroxydiphosphonate uptake on bone scintigraphy in patients with hereditary transthyretin amyloidosis: an early follow-up marker? *Eur J Nucl Med Mol Imaging*. 2024;51(3):681-690. doi:10.1007/s00259-023-06459-y
7. Fontana M, Martinez-Naharro A, Chacko L, et al. Reduction in CMR derived extracellular volume with patisiran indicates cardiac amyloid regression. *JACC Cardiovasc Imaging*. 2021;14(1):189-199. doi:10.1016/j.jcmg.2020.07.043
8. Groothof D, Nienhuis HLA, Bijzet J, et al. Regression of bone-tracer uptake in cardiac transthyretin amyloidosis. *Mayo Clin Proc*. 2020;95(2):417-418. doi:10.1016/j.mayocp.2019.10.036